Birt-Hogg-Dubé Newsletter

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BHDSyndrome.org updates

In addition to our existing Access BHD Literature Database available for download, the Mendeley BHD Literature Database Group can now be used to access all BHD-related scientific publications.
Mendeley is a combination of a desktop free application and a website which helps manage, share and discover research publications.

100, 000 Genomes Project

Familial Pneumothorax has been recently added to the list of disorders that can be recruited to the UK 100,000 Genomes Project. Recruited patients will undergo full genome sequencing and any FLCN mutations identified will be reported back to the referring clinician. Patients with obvious symptoms of BHD should have FLCN mutation testing prior to recruitment to the Project. It is likely, however, that many BHD patients who do not have the typical clinical or radiological features will be identified.

Getting to know you

This quarter meet Wendy Dowling from New Zealand who was diagnosed with BHD in 2014 and Dr Mehdi Mellapour who is based at the University of Syrcause. Dr Mellapour is interested in the interaction of folliculin with heat-sensitive proteins and associated roles in kidney tumourigenesis. The interviews can be found here.

BHD Research Highlights

Noteworthy papers from the last quarter include:

Basic:

Amick *et al*., 2016. C9orf72 binds SMCR8, localizes to lysosomes and regulates mTORC1 signaling. Molecular Biology of the Cell. 2016 Aug 24; pii: mbc.E16-01-0003.

- Amick et al. showed that C9orf72-SMCR8 complex, analogous to FLCN- FNIP, localizes to lysosomes and regulates mTORC1 in an amino acid availability-dependent way. The findings give insights into the functions of this sub-family of DENN domain containing proteins.

Kenyon *et al*., 2016. Expression and knockdown of zebrafish folliculin suggests requirement for embryonic brain morphogenesis. BMC Dev Biol. 2016 Aug 9;16(1):23.

- Kenyon et al. generate a zebrafish BHD model using morpholino oligonucleotides to examine the role of FLCN in zebrafish development and reconcile the expression of FLCN transcripts in the developing embryo with the phenotype associated with the morpholino knock-down of FLCN.

Woodford *et al*., 2016. The FNIP co-chaperones decelerate the Hsp90 chaperone cycle and enhance drug binding. Nat Commun. 2016 Jun 29;7

- Woodford *et al.* report that folliculin-interacting protein (FNIP)1 and FNIP2 act as co-chaperones of Hsp90 by regulating its ATPase activity and chaperoning. They also show that the Aha1 co-chaperone competes with FNIPs and can stimulate Hsp90 ATPase activity.

Siggs *et al*., 2016. Mutation of Fnip1 is associated with B-cell deficiency, cardiomyopathy, and elevated AMPK activity. Proc Natl Acad Sci U S A. 2016 Jun 28;113(26). [Epub 2016 Jun 14].

- Using a new mouse model Siggs *et al.* show that *Fnip1* mutation leads to B-cell deficiency and development of cardiomyopathy with gain-of-function mutations in AMPK supporting the idea that FNIP acts as a negative regulator of AMPK.

Wu *et al*., 2016. FLCN Maintains the Leucine Level in Lysosome to Stimulate mTORC1. PLoS One. 2016 Jun 9;11(6).

- Wu *et al.* show that the suppression of FLCN controls mTORC1 activity by modulating the lysosomal leucine levels. FLCN exerts this new function by regulating the accumulation of the amino acid transporter PAT1 on the lysosome surface.

Zhong *et al*., 2016. Tumor Suppressor Folliculin Regulates mTORC1 through Primary Cilia. J Biol Chem. 2016 May 27; 91(22):11689-97. [Epub 2016 Apr 12].

- Zhong *et* al. show that FLCN is a ciliary protein that regulates mTORC1 through primary cilia. The study shows that in response to flow stress, FLCN recruits the kinase LKB1 to primary cilia for activation of AMPK at the basal bodies, causing mTORC1 down-regulation.

Clinical:

Dow *et al*., 2016. A Novel FLCN c.1489_1490delTG Mutation that Escapes the Nonsense-Mediated Decay System. Annals of Clinical & Laboratory Science. 2016 Sep;46(5):562-5.

- Dow *et al.* reported a novel *FLCN* c.1489_1490delTG (p.Val497Glyfs*22) mutation at the genomic DNA and mRNA levels. The *FLCN* mutation escaped the nonsense-mediated decay system (NMD) because of a premature termination code located in an NMD-incompetent region.

Johannesma *et al*., 2016. Risk of spontaneous pneumothorax due to air travel and diving in patients with Birt–Hogg–Dubé syndrome. SpringerPlus (2016) 5:1506.

- Johannesma *et al.* present a study evaluating the incidence of spontaneous pneumothorax in patients with BHD during or shortly after air travel and diving.

Whitworth *et al*., 2016. Multilocus Inherited Neoplasia Alleles Syndrome: A Case Series and Review. JAMA Oncol. 2016 Mar;2(3):373-9.

- Whitworth *et al.* report five new cases of multiple germline mutations in inherited cancer syndrome genes, three of them involve the combination of mutations in FLCN with NF1, TP53, and MSH2.

To participate in an interview feature, submit information or suggest a topic for the next newsletter, please contact us at contact@BHDSyndrome.org.

BHD foundation